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(54) Title: PEPTIDE/PROTEIN SUSPENDED FORMULATIONS																								
<table border="1"><caption>Approximate data points from the graph</caption><thead><tr><th>Time (Days)</th><th>Value</th></tr></thead><tbody><tr><td>5</td><td>0</td></tr><tr><td>10</td><td>4</td></tr><tr><td>15</td><td>7</td></tr><tr><td>20</td><td>10</td></tr><tr><td>25</td><td>13</td></tr><tr><td>30</td><td>15</td></tr><tr><td>35</td><td>17</td></tr><tr><td>40</td><td>18</td></tr><tr><td>45</td><td>19</td></tr><tr><td>48</td><td>20</td></tr></tbody></table>			Time (Days)	Value	5	0	10	4	15	7	20	10	25	13	30	15	35	17	40	18	45	19	48	20
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(57) Abstract The present invention provides improved compositions for improving the chemical and physical stability of peptides and proteins. The invention provides a liquid beneficial agent formulation containing a liquid suspension comprising at least 5 % by weight beneficial agent and having a viscosity and beneficial agent size which minimizes setting of the agent in suspension over the extended delivery period.																								

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PEPTIDE/PROTEIN SUSPENDING FORMULATIONS

TECHNICAL FIELD

This invention relates to stabilized, concentrated suspensions formulations of peptides and proteins. More particularly, this invention relates to novel and improved compositions for providing concentrated, non-aqueous suspensions of peptides/proteins for pharmaceutical use having adequate chemical, physical and bioactive stability suitable for long term delivery from a sustained release drug delivery system.

BACKGROUND ART

Proteins, as well as many other biologically active compounds, degrade over time in aqueous solution. Because of this chemical instability, protein solutions are often not suitable for use in drug delivery devices. Carriers, in which proteins do not dissolve but rather are suspended, can often offer improved chemical stability. Furthermore, it can be beneficial to suspend the beneficial agent in a carrier when the agent exhibits low solubility in the desired vehicle. However, suspensions can have poor physical stability due to settling and agglomeration of the suspended beneficial agent. The problems with non-aqueous carriers tend to be exacerbated as the concentration of the active compound is increased.

For drug delivering implants, dosing durations of up to one year are not unusual. Beneficial agents which have low therapeutic delivery rates are prime candidates for use in implants. When the device is implanted or stored, settling of the beneficial agent in the liquid formulation can occur. This heterogeneity can adversely effect the concentration of the beneficial agent dispensed. Compounding this problem is the size of the implanted beneficial agent reservoir. Implant reservoirs are generally on the order of

1 25-250 μ l. With this volume restriction, a formulation of high concentration
2 (greater than or equal to 10%) and a minimum amount of suspension vehicle
3 and other excipients is preferred.

4 Alpha interferon (α -IFN) is one example of a beneficial agent which
5 provides a therapeutic effect at a low dose. This interferon is indicated in the
6 treatment of chronic hepatitis because of its antiviral activity. Prescribed
7 therapy presently entails injections of α -IFN solution, containing about
8 3.0×10^6 IU (15 micrograms) of agent per dose, three times per week for a
9 4 to 6 month period. Frequent injections are required because of the short
10 elimination half-life of α -IFN; most of the drug being completely cleared from
11 the plasma within eight to ten hours after the injection.

12 U.S. Pat. Nos. 4,871,538 issued to Yim et al; 4,847,079 issued to
13 Kwan et al; 5,081,156 issued to Yamashira et al, and European Publication
14 No. 0,281,299 issued to Yim et al describe IFN /peptide compositions with
15 concentrations between 10^4 to 10^8 IU/ml. In Kwan et al, a pharmaceutical
16 solution having a α -IFN concentration of 10^3 to 10^8 IU/ml is described.
17 Yim describes a dosage range being between 10^4 to 10^8 IU α -IFN/ml.
18 In Yim II, an insoluble complex including α -IFN, zinc, and protamine is
19 suspended in a phosphate buffer. Yim I, Yim II, and Kwan, however, teach
20 the use, in part, of an aqueous buffer in their compositions. This leads to
21 possible hydrolysis of the compound, leading to chemical degradation and
22 instability. Yamashira teaches a sustained release preparation of interferon in
23 a mixture with a biodegradable carrier. IFN is incorporated at concentrations
24 of 10^3 to 10^8 IU per 1 mg of carrier or, alternatively, each dosage form
25 containing 10^4 to 10^8 IU of interferon. Furthermore, while the patents and
26 publications described above describe concentrations between 10^4 to 10^8
27 IU/ml, none describe concentrations on the order of 10^9 to 10^{11} IU/ml.

1 There is a need for a novel composition comprising a nonaqueous
2 suspension vehicle and concentrated protein/peptide as the beneficial agent
3 for use in implanted, sustained release devices. While it is known in the art to
4 achieve stable α IFN concentrations of up to 10^8 IU/ml, this invention utilizes a
5 novel combination whose combined effect produces a significant and
6 surprising improvement in the physical and chemical stability of the beneficial
7 agent compound over other formulations.

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BRIEF DESCRIPTION OF THE DRAWINGS

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FIG. 1 is a cross-section of an implantable sustained release osmotic
delivery device for use in combination with the concentrated suspensions of
the present invention.

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FIG. 2 is a graph illustrating the stability of a cytochrome c suspension.

FIG. 3 is a graph illustrating the stability of an α -interferon suspension.

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DESCRIPTION OF THE INVENTION

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One aspect of this invention relates to preparations for stabilizing
peptides and proteins at high concentrations for extended periods of time.

Another aspect of this invention relates to stabilized preparations of
human α -IFN.

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Another aspect of this invention relates to stabilized preparations of
human α -IFN having concentrations of at least 1×10^9 IU/ml.

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Another aspect of this invention relates to stabilizing beneficial agent
formulations comprising a beneficial agent having a particle size of between
0.3 to 50 microns and suspension vehicle formula having a viscosity between
100 to 100,000 poise at 37°C.

1 The new formulations are physically stable suspensions which provide
2 chemical stability to water sensitive compounds and can be employed to
3 stabilize high concentrations of the active compound. The carrier
4 components are acceptable for use in implantable systems.

5

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MODES FOR CARRYING OUT THE INVENTION

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8 The concentrated beneficial agent suspensions of the present
9 invention provide significantly stable concentrations over extended periods of
10 time, useful for sustained delivery, implant applications. The suspensions of
11 this invention minimize the particle degradation due to hydrolysis and particle
12 settling over the duration of the extended delivery period. These extended
13 periods of time are between one week to two years, preferably between three
14 months to one year.

15 The sustained parenteral delivery of drugs provides many advantages.

16 Typical sustained release implantable osmotic delivery devices are
17 described in U.S. Pat. Nos. 5,034,229; 5,057,318; and 5,110,596 which are
18 incorporated herein by reference. As shown in Fig. 1, these devices 10
19 typically comprise a housing 12 including a fluid impermeable wall section 14
20 and a fluid permeable wall section 6 which sections define and surround an
21 internal compartment 18. An exit passageway 20 is formed within the fluid
22 impermeable wall section to fluidly communicate the internal compartment 18
23 with the external environment. To minimize exposure to the environmental
24 fluids, a beneficial agent 22 is contained within the fluid impermeable section.
25 An expandable driving member 24, contained within the fluid permeable
26 section, expands with the imbibition of fluid across the fluid permeable wall
27 section. Typically a piston 26 separates the beneficial agent 22 from the
28 expandable driving member 24. This forces the agent out through the exit

1 passageway and into the environment of use. The non-aqueous
2 administration of a beneficial agent in the suspension formulation as
3 disclosed herein can be accomplished using implant devices of these kinds.

4 According to this invention, high concentrations of the beneficial agent
5 remain suspended, and physically and chemically stable in a non-aqueous
6 suspension vehicle. "High concentration" is defined as the beneficial agent
7 concentration level of at least about 0.5 wt% of the formulation, preferably
8 at least about 5 wt% and most preferably between about 10 to 70% w/w.
9 For example, "high concentrations" of α -IFN are 10^9 to 10^{11} IU; and for
10 salmon calcitonin, concentrations of between 2×10^4 IU to 2.8×10^6 IU
11 are "high concentrations". The beneficial agent particle size is between
12 0.3 to 50 microns, and preferably about 1-10 microns in diameter. Desired
13 particle size can be provided typically by milling, sieving, spray drying,
14 supercritical fluid extraction of the particular beneficial agent selected.

15 Typical beneficial agents for use in this device and composition include the
16 interferons and calcitonin. Other representative beneficial agents that can be
17 administered include pharmacologically active peptides and proteins, anabolic
18 hormones, growth promoting hormones, hormones related to the endocrine
19 system comprising porcine growth promoting hormone, bovine growth
20 promoting hormone, equine growth promoting hormone, ovine growth
21 promoting hormone, human growth promoting hormone, growth promoting
22 hormones derived by extraction and concentration from pituitary and
23 hypothalamus glands, growth promoting hormones produced by recombinant
24 DNA methods, bovine growth promoting hormone as described in Nucleic
25 Acid Res., Vol. 10, p 7197 (1982), ovine growth promoting hormone as
26 described in Arch. Biochem. Biophys., Vol. 156, p 493 (1973), and porcine
27 growth promoting hormone as described in DNA, Vol. 2, pp 37, 45, (1983).
28 Representative beneficial agents also comprise coxichine, cosyntropin,
29 and lyppressin. The polypeptides also comprise growth hormone, somatropin,
30 somatotropin, somatotropin analogues, modified porcine somatotropin,

1 modified bovine somatotropin, derivatives of both porcine and bovine
2 somatotropin, somatomedin-C, gonadotropic releasing hormone, follicle
3 stimulating hormone, luteinizing hormone, LH-RH, LH-RH analogs, growth
4 hormone releasing factor, gonadotropin releasing factor, insulin, chorionic
5 gonadotropin, oxytocin, somatotropin plus an amino acid, vasopressin,
6 adrenocorticotrophic hormone, epidermal growth factor, prolactin,
7 somatostatin, somatotropin plus a protein, polypeptides such as thyrotropin
8 releasing hormone, thyroid stimulating hormone, secretin, pancreozymin,
9 enkephalin, glucagon, endocrine agents secreted internally and distributed in
10 an animal by way of the bloodstream, and the like. The beneficial agents and
11 their dosage unit amounts are known to the prior art in The Pharmacological
12 Basis of Therapeutics, by Gilman, Goodman, Rall and Murad, 7th Ed., (1985)
13 published by MacMillan Publishing Co., NY; in Pharmaceutical Sciences,
14 Remington, 17th Ed., (1985) published by Mack Publishing Co., Easton, PA,
15 and in U.S. Pat. No. 4,526,938. Particularly preferred are beneficial agents
16 which produce the desired therapeutic effect at a low delivery rate/dose,
17 for example, proteins/peptides which require picograms to milligrams of
18 agent.

19 A pharmaceutically acceptable suspension vehicle is used to suspend
20 the solid beneficial agent particles in the beneficial agent formulation.
21 Non-aqueous vehicles are used to isolate the beneficial agent from water and
22 prevent hydrolysis or other degradation of the beneficial agent while in
23 suspension. Furthermore, pharmaceutically acceptable suspension vehicles
24 may function as a thickening agent for the components present in an implant.
25 As a vehicle for transporting beneficial agents from the implant, it provides
26 protection against the decomposition of a beneficial agent, and it imparts
27 physical and chemical stability to components present in the formulation.
28 The thickening agent may be used to increase the viscosity of the formulation
29 to prevent fluids in the implantation environment from mixing with the

1 implant's beneficial agent formulation. The amount of thickening agent
2 present in the formulation is between 1% to 99.9% and preferably 5-60%
3 depending upon the viscosity adjustment needed.

4 Typical non-aqueous suspension vehicles include: waxes, which have
5 a softening temperature at or less than body temperature; hydrogenated
6 vegetable oils, (e.g., peanut oil, cottonseed oil, sesame oil, castor oil, olive oil,
7 corn oil, iodinated poppy seed oils) silicon oil, medium chain fatty acid
8 monoglycerides, or polyols. Of these polyols are preferred.

9 Polyols suitable for suspension vehicles include such as diol, triol,
10 polyhydric alcohol, and the like. More specific polyols comprise polyethylene
11 glycol (average molecular weight between 200 and 1000), propylene glycol,
12 polyethylene glycol 1,5-pentylene glycol; 1,6-hexylene glycol; 1,7-heptylene
13 glycol; 1,9-nonylene glycol; 1,2-dimethyl-1,6-hexylene glycol;
14 1,2,3-propanetriol; 1,2,5-pentanetriol; 1,3,5-pentanetriol; 1,2,4-butanetriol;
15 dipentaerythriol, and the like. In another embodiment the pharmaceutically
16 acceptable suspension vehicle comprises glycerol mono(lower alkyl) ethers
17 and glycerol di(lower alkyl) ethers such as glycerol 1-methyl ether; glycerol
18 1-ethyl ether; glycerol 1,2-dimethyl ether; glycerol 1,3-dimethyl ether,
19 and the like. In another embodiment the pharmaceutically acceptable vehicle
20 comprises a mixture such as propylene glycol and glycerol, and the like.

21 Sufficient viscosity is required to suspend the particles in the carrier
22 throughout the duration of the extended delivery period. Settling is a function
23 of the particle size and the carrier viscosity. If the duration of the delivery
24 period is shorter, the viscosity can be lower since the time required to be

1 suspended is shorter. The viscosity required, for example, can be determined
2 by the Stokes-Einstein equation which is a measure of how far a particle in
3 suspension will travel

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5
$$V = \frac{2gR^2 (P_p - P_c)}{9\mu}$$

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7

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9 V = velocity of settling
10 μ = viscosity of the carrier
11 g = acceleration due to gravity
12 P_p = density of particle
13 P_c = density of carrier
14

15 wherein R = the average particle radius of the beneficial agent. The viscosity
16 of the beneficial agent suspending formulation can be altered by the use of
17 thickening agents to raise the viscosity to the desired level. Typical
18 thickening agents for use in the compositions of this invention include suitable
19 hydrogels such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose
20 (HPMC), sodium carboxymethyl cellulose, polyacrylic acid, poly(methyl
21 methacrylic acid) (PMMA). Preferred hydrogels are cellulose ethers such as
22 hydroxyalkylcellulose and hydroxyalkylalkyl-cellulose compounds. A most
23 preferred hydroxyalkylcellulose is hydroxypropyl cellulose (HPC) and
24 povidone (PVP). Hydroxypropyl cellulose is commercially available in a wide
25 range of viscosity grades sold under the tradename Klucel™ (Hercules, Ltd.,
26 London, England). The concentration of the hydroxyalkylcellulose is
27 dependent upon the particular viscosity grade used and the desired viscosity
28 of the liquid composition. For example, where the desired viscosity is less
29 than about 1000 poise (cps), hydroxypropyl cellulose having an average
30 molecular weight of about 60,000 daltons (i.e., Klucel EF™) can be used.
31 Where the desired viscosity is from about 1000 to about 2500 cps, higher
32 viscosity grades of hydroxypropyl cellulose can be used (i.e., Klucel LF™ and
33 Lucel GF™). In addition to using different viscosities of different thickening

1 agents, using different amounts of the same particular thickening agent can
2 be used to vary the viscosity. Preferably, the concentration of hydroxypropyl
3 cellulose is from 5 percent w/w and, more preferably from 5 to 20 %w/w of the
4 carrier and most preferably between 8-18 %w/w. Aluminum monostearate
5 can be used as a thickening agent if oils are used as the carrier.

6 Hydroxyalkylalkylcellulose ethers are a class of water-soluble
7 hydrogels derived from etherification of cellulose. As used herein in reference
8 to this class of hydrogels, the term "alkyl" means C₁-C₆ alkyl where alkyl
9 refers to linear or branched chains having 1 to 6 carbon atoms, which can be
10 optionally substituted as herein-defined. Representative alkyl groups include
11 methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl and the like.

12 Exemplary hydroxyalkylalkylcelluloses are hydroxypropylmethyl
13 cellulose, hydroxyethylmethyl cellulose and hydroxybutylmethyl cellulose.
14 Hydroxypropylmethyl cellulose (HPMC) is preferred. HPMC is commercially
15 available (i.e., Aldrich Chem. Co., Ltd. Dorset, England and Dow Chem. Co.,
16 Midland, Mich., USA) in a wide range of viscosity grades. In addition to
17 increasing viscosity, hydroxyalkylalkylcelluloses can serve as a stabilizing,
18 suspending and emulsifying agent. The concentration of
19 hydroxyalkylalkylcellulose in a liquid composition of this invention is
20 dependent inter alia on its intended use (i.e., stabilizer, emulsifier,
21 viscosity-increasing agent) and its viscosity grade.

22 To assure the viscosity of the suspension vehicle is sufficient to
23 maintain the agent in suspension over the desired delivery period, thickening
24 agents can be added to the suspension vehicle. The preferred thickening
25 agents include povidone and hydroxypropyl cellulose. In one embodiment,
26 when the PEG utilized is a low molecular weight, e.g., 400, 5% hydroxypropyl
27 cellulose, having an average molecular weight of 1000, or 40 -60% povidone
28 can be used in combination with a balance of polyethylene glycol. If the

1 polyethylene glycol utilized in the suspension vehicle has a molecular weight
2 of greater than 600, e.g., 1000 molecular weight, povidone is preferably
3 utilized as the thickening agent.

4 The following examples are offered to illustrate the practice of the
5 present invention and are not intended to limit the invention in any manner.

6

7

EXAMPLE 1

8

9 A viscous carrier was prepared containing 50% PEG 400 and
10 50% povidone (PVP) by weight. PEG 400 (Union Carbide) was weighed
11 into a beaker and an equal weight of povidone K29-32 (GAF) was added.
12 The PEG and povidone were mixed by stirring with a spatula for about
13 5 minutes. The blended carrier was allowed to sit overnight to insure
14 complete dissolution of the povidone. The carrier was then deaerated in a
15 vacuum oven (National Appliance Company) by drawing a vacuum and
16 holding the carrier at 50°C for 30 minutes.

17 Cytochrome c (Sigma, from horseheart) was milled in a jar mill and
18 then passed through a 400 mesh screen to produce a particle diameter of
19 less than 37 micron. In a beaker, 0.5566 grams of the cytochrome c was
20 added to 4.9970 grams of the PEG 400/povidone carrier to prepare a 10%
21 cytochrome c suspension in 50:50 PVP:PEG 400 carrier. The suspension
22 was thoroughly blended by mixing with a spatula for about 5 minutes.
23 The cytochrome c suspension was then loaded into 11 osmotic veterinary
24 implants (as in Figure 1).

25 The implants were tested in vitro by releasing into culture tubes filled
26 with deionized water. To monitor release of cytochrome c from the implants,
27 samples of the release media were assayed on a UV spectrophotometer
28 (Shimadzu UV 160U) at a wavelength of 409 nm. The implants delivered the
29 cytochrome c successfully over the designed duration of the implant

1 (42 days). Fig. 2 is a graph that illustrates the cumulative protein delivery
2 (mg) over time. During the later half of the release period, several implants
3 were removed from the tubes and examined to determine whether settling of
4 the cytochrome c had occurred. These implants were sectioned and samples
5 of the protein suspension were removed from the top and bottom portions of
6 the implant. The samples of the protein suspension were weighed, diluted
7 with DI water in volumetric flasks and assayed via UV a spectrophotometer.
8 Results indicated that the cytochrome c suspension was homogeneous.

9

10 EXAMPLE 2

11

12 Standard : 20 μ l of a 8.0 mg/ml standard was diluted to 160 μ g/ml.

13 Each HPLC sample was diluted by a factor of 10 into distilled water.

14 The operating conditions of the HPLC were as follows:

15 Column: POROS RH 2.1 mm x 3.0 cm

16 Mobile phase: A: 95% H₂O, 0.1% TFA, 5% ACN

17 B: 95% ACN, 5% H₂O, 0.083% TFA

18 Gradient: 20% B to 50% B in 5 minutes

19 Flow: 2.0 ml/min

20 Detector: 280 nm @ 0.002 AUFS

21 IRMA Standards: Working standards were prepared by diluting IRMA
22 standards into phosphate buffered saline (PBS) containing 0.5% Bovine
23 Serum Albumin (BSA). Samples were prepared by serially diluting by factors
24 of 400 for interferon formulations and 2000 for the standard into PBS
25 containing 0.5% BSA.

26 Figure 3 shows the results of the HPLC and the IRMA assays.

27 The HPLC measurements indicate no losses of the α -IFN over 5 days, even
28 at 37° C, indicating stability of this protein in non-aqueous vehicle. Relative
29 to the initial stock solution, the activity shown by IRMA at $t = 0$ is 78%.

1 At t = 5 days, the formulation displayed an activity of 87% at room
2 temperature and 90% at 37°C. When compared to the original stock,
3 no losses of α -IFN were detected by HPLC in this formulation. Stability
4 of interferon in PEG over 5 days at 37° C was indicated by this assay.
5 However, approximately 80 - 90% of the activity of the initial stock was
6 maintained. The IRMA readings suggest no activity losses due to time and
7 temperature effects.

8 This invention has been described in detail with particular reference
9 to certain preferred embodiments thereof, but it will be understood that
10 variations and modifications can be effected within the spirit and scope of
11 the invention.

1 WHAT IS CLAIMED IS:

2

3 1. A beneficial agent formulation for use in a device which delivers
4 the formulation over an extended delivery period, the formulation comprising
5 a suspension containing at least 5% by weight beneficial agent in the form of
6 solid particles, the beneficial agent particle size being 0.3 to 50 microns and
7 the suspension viscosity being sufficient to prevent settling of the agent in the
8 suspension formulation over the extended delivery period.

9 2. The formulation of claim 1, wherein the particle size is between
10 1 to 10 microns.

11 3. The formulation of claim 1, wherein the viscosity is 100 to
12 100,000 poise at 37°C.

13 4. The formulation of claim 1, wherein the extended delivery period
14 is at least about 1 month.

15 5. The formulation of claim 1, wherein the liquid suspension
16 further comprises a low molecular weight polyol and a thickening agent.

17 6. The formulation of claim 5, wherein the polyol is polyethylene
18 glycol having a molecular weight between 200 and 1000.

19 7. The formulation of claim 6, wherein the thickening agent
20 comprises povidone.

21 8. The formulation of claim 5, wherein the polyol is polyethylene
22 glycol having a molecular weight between 200 and 600.

23 9. The formulation of claim 8, wherein the thickening agent
24 comprises povidone or hydroxypropyl cellulose.

25 10. The formulation of claim 1, wherein the beneficial agent is
26 human α -interferon.

27 11. The formulation of claim 10, wherein the concentration of
28 interferon is at least 1×10^9 IU.

29 12. The formulation of claim 1, wherein said beneficial agent is a
30 water sensitive compound.

1 13. A beneficial agent delivery device containing the formulation of
2 claim 1.

3 14. The beneficial agent delivery device of claim 13, wherein the
4 device is adapted to be implanted within an animal.

5 15. A composition for sustained controlled delivery over an
6 extended delivery period, the composition comprising:

7 (a) 0.5% to 70% by weight beneficial agent having a particle size of
8 between 0.3 to 50 microns; and

9 (b) a non-aqueous liquid suspension formulation characterized by a
10 viscosity of between 100 to 100,000 poise at 37 ° C, the formulation further
11 comprising polyethylene glycol with a molecular weight between 200 and
12 1000 and a thickening agent.

13 16. The composition according to claim 15, wherein the thickening
14 agent comprises povidone or hydroxypropyl cellulose.

15 17. A beneficial agent delivery device containing the composition of
16 claim 15.

17 18. The beneficial agent delivery device of claim 17, wherein the
18 device is adapted to be implanted within an animal.

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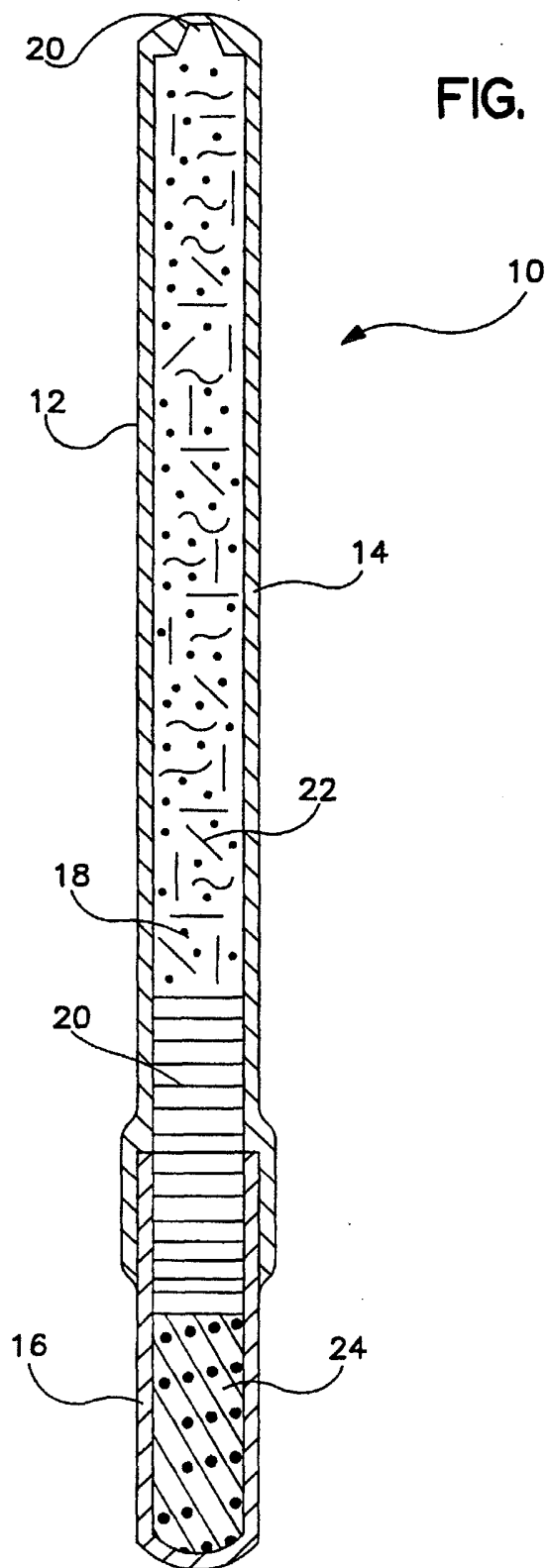
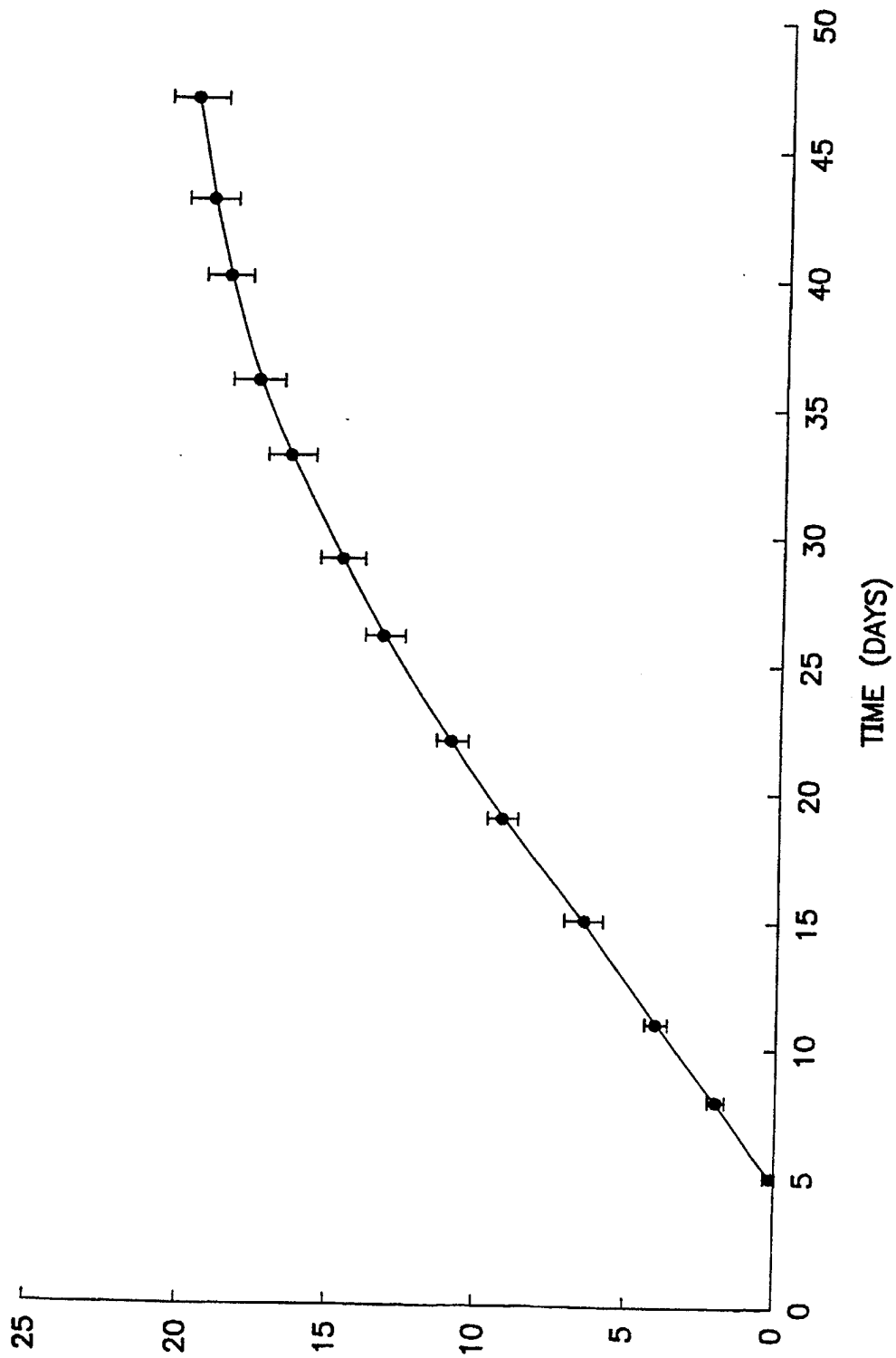
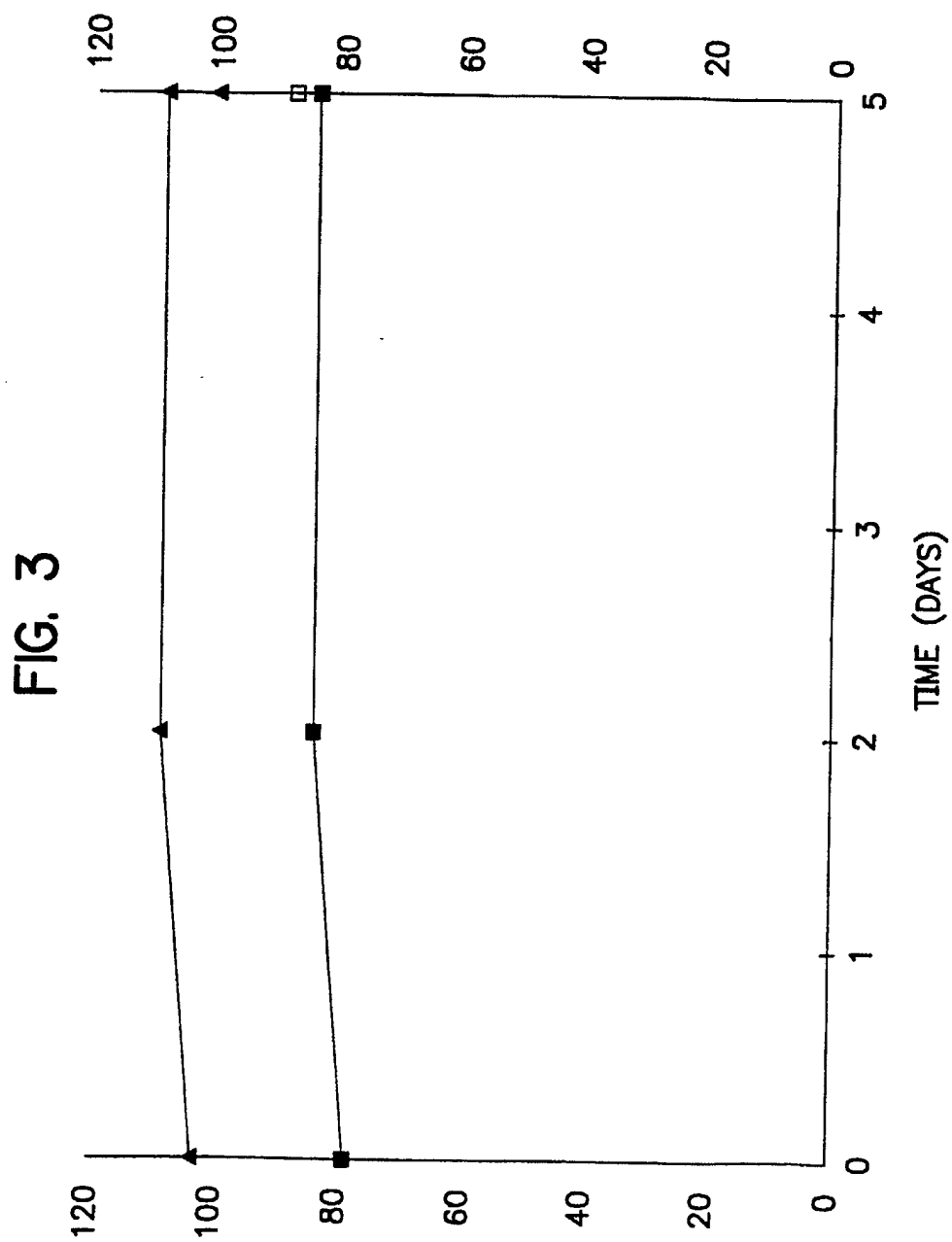


FIG. 2



3 / 3



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/07377

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K9/00 A61K47/10 A61K47/32 A61K47/38		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 374 120 (MONSANTO COMPANY) 20 June 1990	1,3,4, 12-14
Y	see claims 1,7,8 see page 6, line 54 - page 7, line 3 see page 7, column 19 - column 21 see page 7, column 38 - column 40 see page 7, column 50 - column 52 ---	10
X	US,A,4 855 141 (ALZA CORPORATION) 8 August 1989 see claim 1 see column 10, line 22 - column 11, line 15 --- -/--	1,5,12, 13
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 17 September 1996		Date of mailing of the international search report 30.09.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016		Authorized officer Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 96/07377

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	<p>WO,A,95 34285 (ALZA CORPORATION) 21 December 1995 see claims 1,2 see page 14, line 20 - page 16, line 2 see page 20, line 3 - line 11 -----</p>	10

INTERNATIONAL SEARCH REPORT

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